

**REMARKS**

Claims 8 and 10-13 and 17-18 are pending in the application. Claims 14-16 have been newly cancelled herein and the subject matter thereof has been incorporated into claims 8 and 18.

**Substance of the Interview**

Applicants would like to thank Examiners Winkler and Housel for their time and comments during the interview of November 15, 2004. Applicants have considered the discussion with the Examiners and have further addressed the rejections in view of that discussion with the present amendments and remarks.

**Rejections under 35 U.S.C. §103**

In the Office Action, the Examiner maintains the rejection of the claims over Kondo, combined with Harada, and Shirakawa. The Examiner also raises a new prior art rejection of claims 8 and 10-16 over Kondo, combined with Harada, Shirakawa, and the newly cited references of Galle, Dienes and Luo. These rejections are addressed in turn below.

1) Kondo, combined with Harada, and Shirakawa

Kondo is relied on for teaching that a soluble form of Fas prevented CTL-induced liver disease in HbsAg transgenic mice (a model for fulminant hepatitis). Kondo is further relied on for teaching that a soluble form of Fas had a protective effect on the

endotoxin-induced hepatic injury with mice primed with killed *P. acnes* (a second model for fulminant hepatitis).

Both mouse model systems using in Kondo are for fulminant hepatitis, i.e. hepatitis which is typically caused by infection with HBV or HCV. (See page 409, left column of Kondo.) The fact that Kondo considered models for only a specific form of hepatitis, i.e. fulminant hepatitis caused by infectious agents, is an important distinction for consideration of the invention of the presently amended claims.

The present claims have been amended to be specifically drawn to methods for treating primary biliary cirrhosis or bile duct disappearance syndrome caused by an immunological mechanism. As indicated on page 6, beginning at page 6 of the specification, primary biliary cirrhosis is an autoimmune disease. The claims have been amended herein to define the bile duct disappearance syndrome as being immune-based. Thus, the present invention is to methods of treating two specific immune disorders.

As discussed beginning at page 3, 3<sup>rd</sup> paragraph of the specification, cirrhosis is the terminal stage of chronic progressive hepatic diseases of the liver. However, cirrhosis can have numerous unrelated etiological causes including, viral, drug-induced, alcoholic, parasitic, congestive, biliary, Wilson's disease etc. (See page 4, 1<sup>st</sup> paragraph.)

While "cirrhosis" is the final disease state, the etiology of the disease is important in understanding the mechanism of pathology and predicting an efficacious treatment. For example, as discussed on page 8 of the specification, the mechanism apoptosis in viral hepatitis is believed to be different from that in alcoholic cirrhosis. This conclusion is also reported in Galle, which is newly cited by the Examiner.

As noted above, the models in Kondo looked at the possible involvement of Fas/Fas ligand in viral hepatitis. The present invention, on the other hand, is directed specifically to treating immune-based disorders. The conclusions of Kondo regarding viral hepatitis are not predictive of the specific etiology of immune-based pathologies to which the presently amended claims are drawn for several reasons, as detailed below.

a) First, as discussed above and in the specification, it was accepted in the field of the invention that pathologies having different etiologies might have different apoptotic mechanisms. Thus, the conclusions reached by Kondo are not predictive of the involvement of Fas/Fas ligand in the specific diseases to which the invention has been limited.

b) A second very important consideration is that other immune-based disorders involving Fas/Fas ligand, which one might also think to be predictive of the mechanism involved with primary biliary cirrhosis and bile duct disappearance syndrome caused by an

immunological mechanism, have been found to be responsive to treatment with a Fas agonist, i.e. the complete opposite to the claimed invention.

Indeed, if the role of Fas/Fas ligand in other immune-based pathologies is considered, one skilled in the art would conclude that it would more likely be desirable to treat PBC-related pathologies by inducing apoptosis. For example, WO 95/32627 teaches that Fas agonists (in this case Fas ligand) are useful in treating transplantation rejection, diabetes, rheumatoid arthritis (RA), multiple sclerosis, cystic fibrosis etc. EP 0709097 similarly teaches that Fas agonists (in this case anti-Fas antibody) are useful for treating rheumatoid disorders, such as RA.

The Examiner relies further relies on Harada in support of the rejection. However, while Harada studied PBC, Harada does not provide any prediction of the mechanistic involvement of Fas/Fas ligand in PBC. Harada looked at CD95 and CD95 ligand expression; however, even showing an increased level of expression of CD95 expression does not answer the critical question of whether a Fas antagonist or Fas agonist is necessary for treating PBC. Neither does Shirakawa assist in predicting the method of the invention. Shirakawa discloses antibodies that can act as a Fas antagonist and antibodies that can act as a Fas agonist. However, as acknowledged by the Examiner, there is no disclosure in Shirakawa of PBC or of

bile duct disappearance syndrome caused by an immunological mechanism.

c) As a third important overall consideration, and as Applicants discussed in previous responses and during the interview, the potential role of Fas/Fas ligand and the mechanism of pathology in different hepatic pathologies was highly controversial at the time of the invention. The Examiners and Applicants appear to differ on this point. However, the Examiner is requested to again consider this point in view of the present claim amendments and comments above.

As discussed previously, different equally reputable journals reached differing conclusions regarding the involvement of Fas/Fas ligand in PBC based on the exact same consideration, i.e. the expression of Fas. Harada reported an upregulation of Fas expression in PBC and from the concluded that Fas is involved in PBC apoptosis. However, Graham reported no change in Fas expression and concluded that Fas was not likely involved in PBC. As indicated above, the studies in Kondo are not predictive of the pathologies of the amended claims, because it was known that different cirrhosis etiologies involved different mechanisms for the pathology.

The controversy and unpredictability is further evident from the references upon which the Examiner relies. For example, even Kondo had to come up with an explanation within their own article

for why perforin-null mice are resistant to lymphocytic choriomeningitis virus (LCMV)-induced hepatitis and do not develop hepatitis in the a mouse model for HBV-mediated hepatitis.

Given the considerations discussed above and the current amendments made to the claims, Applicants believe that the invention as presently claimed, could not be predicted from the prior art and therefore is not obvious over the cited prior art. Withdrawal of the rejection is therefore respectfully requested.

2) Kondo, combined with Harada, Shirakawa and the newly cited references of Galle, Dienes and Luo

Galle et al. is relied on for teaching the absence of Fas RNA in normal liver but the presence of Fas RNA in damaged liver. Galle et al. is further asserted to teach that anti-Fas antibodies induce apoptic cell death of primary hepatocytes.

Dienes et al. is asserted to teach bile duct epithelial cells in primary biliary cirrhosis express Fas.

Luo et al. is asserted to teach the up regulation of Fas in hepatocytes with hepatitis.

The Examiner relies on the new references for the overall teachings of the presence of Fas in primary biliary cirrhosis. The Examiner further asserts that since bile duct disappearance is caused by primary biliary cirrhosis, the same mechanism would be involved with both pathologies. However, the newly cited

references are cumulative with the earlier cited references and have the same failure of the other references of showing a direct involvement of Fas-mediated apoptosis in the progression of the disease states.

In addition, both Galle and Luo, consider viral-induced hepatitis, which, as discussed above, is not predictive of the specific pathologies of the amended claims. In addition, Dienes, like Harada only looks at CD95 expression in PBC, thus this reference is cumulative with Harada.

At the time of the invention it was completely unknown with the pathology of primary biliary cirrhosis (PBC), whether Fas-mediated apoptosis makes the pathology better or worse, when Fas ligand binds to Fas on biliary epithelial cells. Thus, it was not known whether it was more desirable to inhibit Fas-mediated apoptosis (with a Fas antagonist) or to induce Fas-mediated apoptosis (with a Fas agonist). The present invention for the first time, has considered this issue directly and has for the first time achieved a method of treating hepatic cirrhosis or bile duct disappearance syndrome by inhibiting Fas-mediated apoptosis (claim 8). Thus, the present invention is not obvious over cited references of the Examiner and withdrawal of the rejections and allowance of the claims are respectfully requested.

Should there be any outstanding matters that need to be resolved in the present application, the Examiner is respectfully

requested to contact MaryAnne Armstrong, PhD (Reg. No. 40,069) at the telephone number below, to conduct an interview in an effort to expedite prosecution in connection with the present application.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37 C.F.R. § 1.16 or under 37 C.F.R. § 1.17; particularly, extension of time fees.

Respectfully submitted,

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